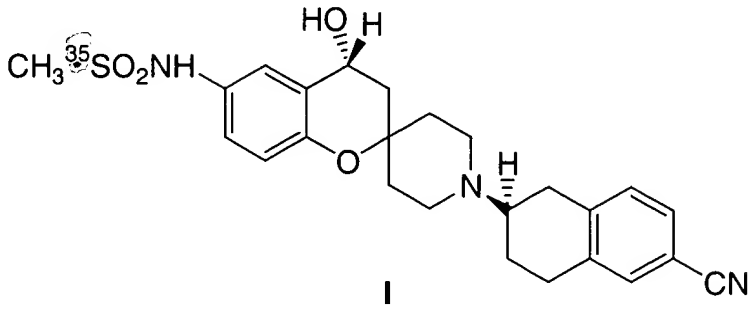
WHAT IS CLAIMED IS:

1. A radioligand compound of Formula I which is



I

or pharmaceutically acceptable salts thereof.

2. The radioligand compound of Formula I, as recited in Claim 1, which possesses a specific activity of greater than 500 Ci/mmol.

3. The radioligand compound of Formula I, as recited in Claim 1, which possesses a specific activity of in the range of about 900 Ci/mmol. to about 1498 Ci/mmol.

4. A method of characterizing an ion channel as an I_{Kr} channel comprising contacting the ion channel with the radioligand compound of Claim 1 and determining if the radioligand compound binds to the ion channel.

5. A method for characterizing the activity of a compound as an I_{Kr} channel blocker comprising contacting the test compound with a membrane containing the I_{Kr} channel in the presence of the radioligand compound of Claim 1 and monitoring whether the test compound influences the binding of the radioligand compound to the membrane containing the I_{Kr} channel.

6. The method as recited in Claim 5, wherein the membrane containing the I_{Kr} channel is derived from a cell line transfected with the ERG gene.

7. The method as recited in Claim 6, wherein the cell line is HEK 293 cells or CHO cells.

8. The method as recited in Claim 7, wherein the ERG gene is human, canine or primate.

9. The method as recited in Claim 8, wherein the radioligand compound of Formula I possesses a specific activity of in the range of about 900 Ci/mmol. to about 1498 Ci/mmol.

10. A method for assessing the binding of a test compound to a membrane containing the I_{Kr} channel using a radioligand compound of Formula I, [^{35}S]-radiolabeled (+)-N-[1'-(6-cyano-1,2,3,4-tetrahydro-2(R)-naphthalenyl)-3,4-dihydro-4(R)-hydoxyspiro[2H-1-benzopyran-2,4'-piperidin]-6-yl]-methanesulfonamide, comprising the steps of:

1) preparing solutions of the test compound at 5 or more different concentrations, a solution of control vehicle and a solution of (+)-N-[1'-(6-cyano-1,2,3,4-tetrahydro-2(R)-naphthalenyl)-3,4-dihydro-4(R)-hydoxyspiro[2H-1-benzopyran-2,4'-piperidin]-6-yl]-methanesulfonamide (compound of Formula II) in a solvent;

2) mixing the radioligand compound of Formula I with the membrane containing the I_{Kr} channel diluted with an assay buffer to form a membrane/radioligand mixture of known concentration;

3) incubating a quantity of known concentration of the membrane/radioligand mixture with the solution of test compound, control vehicle or compound of Formula II, as recited in Step 1, for a set time period at a temperature range of between about 4°C and about 37°C to give a mixture of membrane bound with the radioligand and the test compound, the control vehicle or the compound of Formula II, where the final concentration of the membrane containing the I_{Kr} channel is predetermined;

4) isolating from the incubated mixture the membrane bound with the radioligand and the test compound, the control vehicle or the compound of Formula II;

5) measuring the radioactivity of the isolated membrane bound with the radioligand and the test compound, the control vehicle or the compound of Formula II;

6) repeating steps 3 through 5 with the test compound at each concentration, the solution of control vehicle and the solution of the compound of Formula II, as recited in Step 1; and

7) calculating the IC_{50} corresponding to the measured radioactivity of: 1) the membrane bound with the radioligand and each concentration of the test compound, 2) the membrane bound with the radioligand and with the control vehicle, and 3) the membrane bound with the radioligand and the compound of Formula II.

correlation step 7.

11. The method as recited in Claim 10, wherein the membrane containing the I_{Kr} channel is derived from a cell line transfected with the ERG gene.

12. The method as recited in Claim 11, wherein the cell line is HEK 293 cells or CHO cells.

13. The method as recited in Claim 12, wherein the ERG gene is human, canine or primate.

14. The method as recited in Claim 13, wherein the solutions of the test compound are prepared in Step 1 at 7 different concentrations.

15. The method as recited in Claim 14, wherein the time period for incubation in Step 3, is about 30 minutes to 1 hour.

16. The method as recited in Claim 15, wherein the temperature for the incubation in Step 3, is room temperature (25°C).

17. The method as recited in Claim 16, wherein the membrane-bound with radioligand or test compound is isolated in Step 4 with Unifilters, Scintillation Proximity Assay (SPA) beads or the Flashplates.

18. The method as recited in Claim 17, wherein the membrane containing the I_{Kr} channel is derived from a HEK 293 cell line transfected with the human ERG gene.

19. The method as recited in Claim 8, wherein the radioligand compound of Formula I possesses a specific activity of in the range of about 900 Ci/mmol. to about 1498 Ci/mmol.

20. A method for assessing the binding of a test compound to a membrane containing the I_{Kr} channel using a radioligand of Formula I, [^{35}S]-radiolabeled (+)-N-[1'-(6-cyano-1,2,3,4-tetrahydro-2(R)-naphthalenyl)-3,4-dihydro-4(R)-hydoxyspiro[2H-1-benzopyran-2,4'-piperidin]-6-yl]-methanesulfonamide, comprising the steps of:

1) preparing assay wells with 4 μl of the test compound in dimethylsulfoxide (DMSO) diluted 100x with assay buffer at 5 or more different concentrations, a control vehicle of DMSO and a DMSO solution of (+)-N-[1'-(6-cyano-1,2,3,4-tetrahydro-2(R)-naphthalenyl)-3,4-dihydro-4(R)-hydoxyspiro[2H-1-benzopyran-2,4'-piperidin]-6-yl]-methanesulfonamide (compound of Formula II);

2) adding the radioligand compound of Formula I at 50pM to the membrane containing the I_{Kr} channel diluted with assay buffer to form a membrane/radioligand mixture;

3) incubating each assay well with 400 μl of the 50 pM membrane/radioligand mixture for about 75 minutes to about 90 minutes at room temperature (25^{o}C) to give assay wells containing the membrane bound with the radioligand and the test compound at each concentration, the DMSO control vehicle or the compound of Formula II where the final concentration of the membrane containing the I_{Kr} channel is 11μg/ml;

4) filtering the incubated assay wells through 0.1% BSA presoaked filters to isolate on the filters the membrane bound with the radioligand and the test compound at each concentration, the DMSO control vehicle or the compound of Formula II;

5) washing each of the filters containing the membrane bound with the radioligand and the test compound at each concentration, the DMSO control vehicle or the compound of Formula II about 5 times with 500 μl of ice cold wash buffer;

6) drying the washed-filters containing the membrane bound with the radioligand and the test compound at each concentration, the DMSO control vehicle or the compound of Formula II at room temperature in a fume hood;

7) adding 50 µl Microscint-20 microscintillate to the dried-filters containing the membrane bound with the radioligand and the test compound at each concentration, the DMSO control vehicle or the compound of Formula II;

8) measuring the microscintillation count of the microscintillation-treated filters containing the membrane bound with the radioligand and the test compound at each concentration, the DMSO control vehicle or the compound of Formula II for one minute; and

9) calculating the IC_{50} corresponding to the measured microscintillation count of: 1) the microscintillation-treated filters containing the membrane bound with the radioligand and each concentration of the test compound, 2) the microscintillation-treated filters containing the membrane bound with the radioligand and with the control vehicle, and 3) the microscintillation-treated filters containing the membrane bound with the radioligand and the compound of Formula II.

correlation

21. The method as recited in Claim 20, wherein the membrane containing the I_{Kr} channel is derived from a cell line transfected with the ERG gene.

22. The method as recited in Claim 21, wherein the cell line is HEK 293 cells.

23. The method as recited in Claim 22, wherein the ERG gene is human or canine.

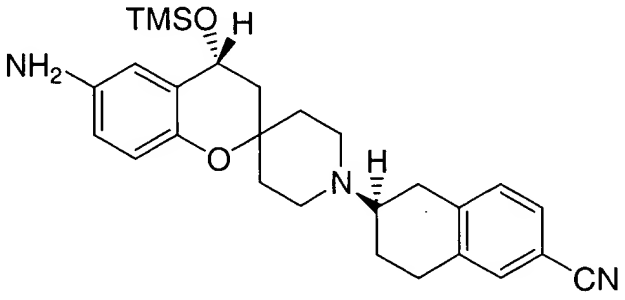
24. The method as recited in Claim 23, wherein the solutions of the test compound are prepared in Step 1 at 7 different concentrations.

25. The method as recited in Claim 24, wherein the membrane containing the I_{Kr} channel is derived from a HEK 293 cell line transfected with the human ERG gene.

26. The method as recited in Claim 25, wherein the radioligand compound of Formula I possesses a specific activity of in the range of about 900 Ci/mmol. to about 1498 Ci/mmol.

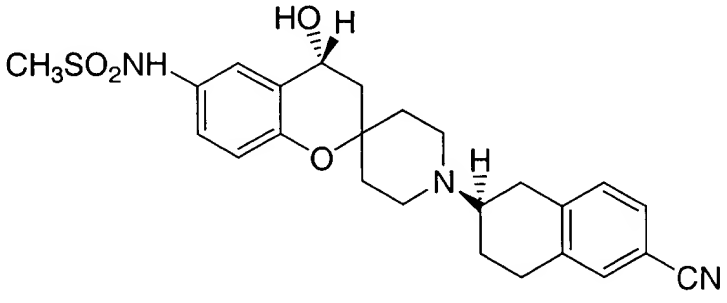
27. The method as recited in Claim 26, wherein the membrane-bound with radioligand or test compound is filtered in Step 4 with Unifilters.

28. A process for the preparation of

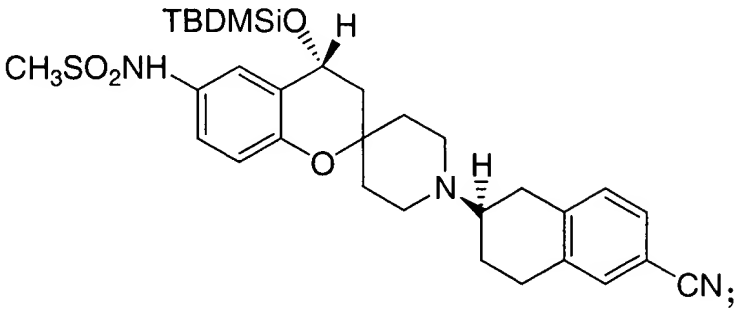


comprising the steps of

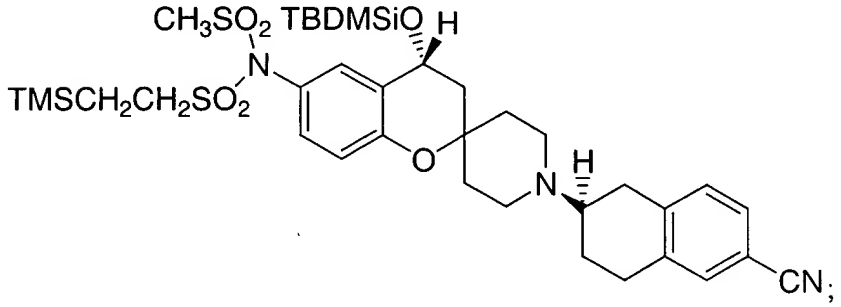
(1) reacting the alcohol with 2,6-lutidine and t-butyldimethylsilyl triflate



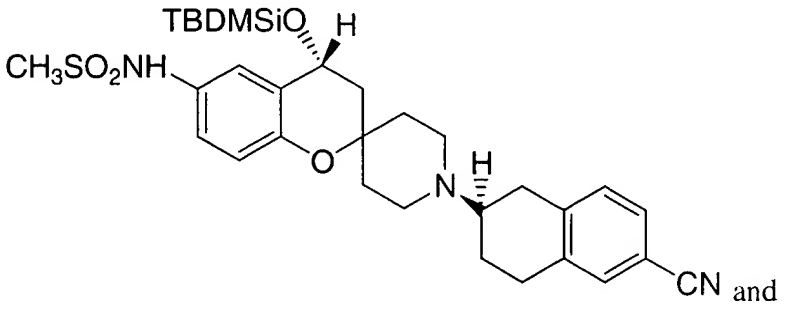
to give a t-butyldimethylsilyl-protected hydroxyl compound



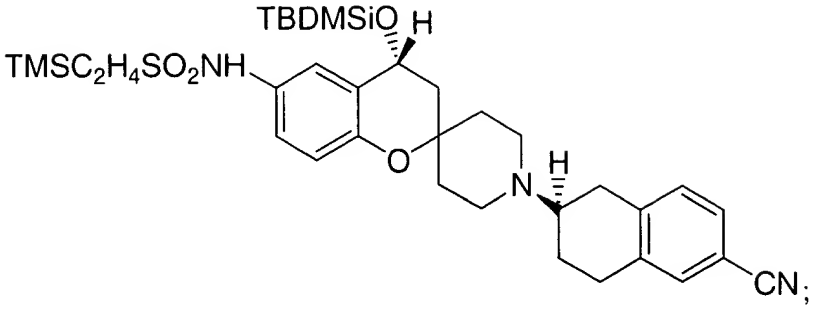
(2) alkylating the t-butyldimethylsilyl-protected hydroxyl compound by treating with sodium hydride, and then treating with 2-trimethylsilylethanesulfonylchloride to give the disubstituted sulfonamide compound



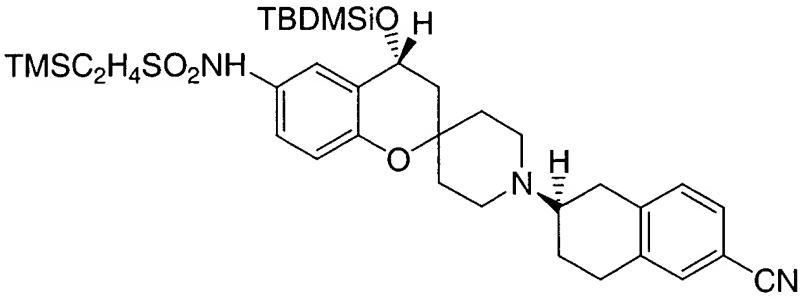
(3) treating the disulfonamide with an C_1-C_8-alkanethiolate to give a mixture of the following sulfonamides;



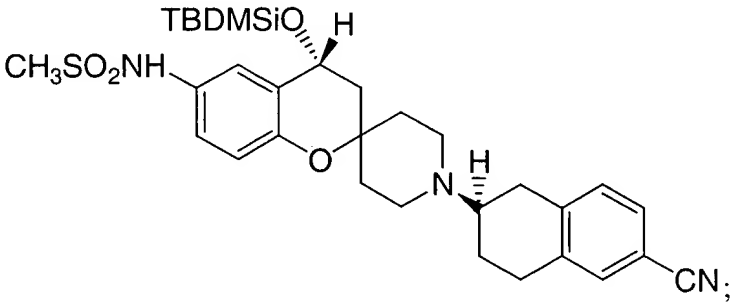
and



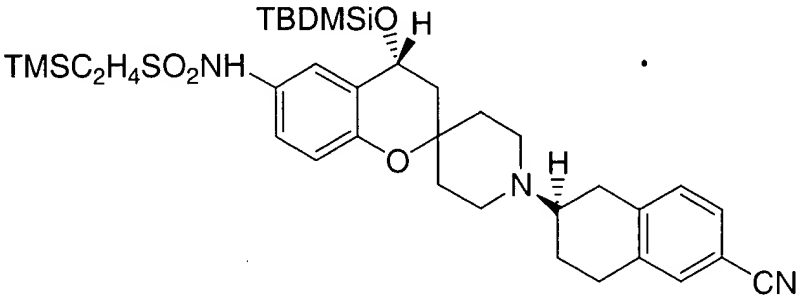
(4) separating the sulfonamide mixture using chromatography to isolate the non-polar sulfonamide eluting with a non-polar solvent system



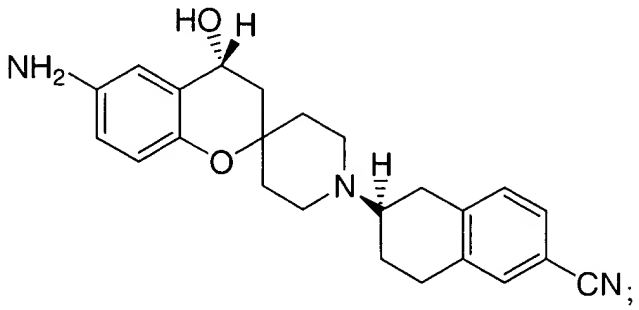
and then eluting off the polar isomer using a polar solvent system



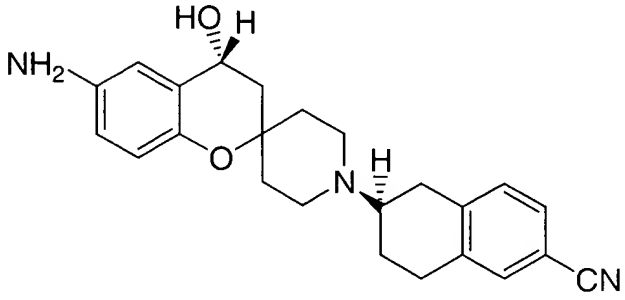
(5) desulfonating the non-polar isomer



using a fluoride compound in an organic base and heating for about 24 hours to about 48 hours to give the free alcohol-amine



(6) reacting the free alcohol-amine with trimethylsilyl imidazole in an organic solvent



to give the desired trimethylsilyloxy compound.

29. The process as recited in Claim 28, wherein the alkylation in step 2 is stirred at room temperature for up to 24 hours.

30. The process as recited in Claim 29, wherein the C_1-C_8-alkanethiolate in step 3 is sodium methanethiolate, sodium ethanethiolate, sodium propanethiolate or sodium 2-methylpropanethiolate.

31. The process as recited in Claim 30, wherein the desulfonylation reaction in step 3 is run for less than 24 hours.

32. The process as recited in Claim 31, wherein the separation of the sulfonamide mixture in step 4 is run using flash chromatography with a solvent system of ethyl acetate and hexane to ethyl acetate and methanol.

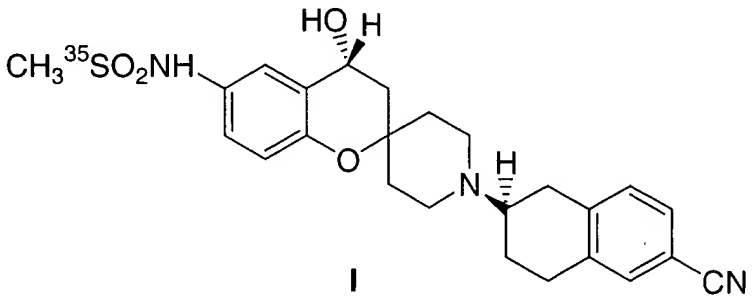
33. The process as recited in Claim 32, wherein the separation of the sulfonamide mixture in step 4 is run using flash chromatography with a non-polar solvent system of 1:1 ethyl acetate: hexane to a polar solvent system of 99:1 ethyl acetate: methanol.

34. The process as recited in Claim 33, wherein The fluoride compound used in the desulfonylation of step 5 is selected from: cesium fluoride and tetrabutylammonium fluoride.

35. The process as recited in Claim 34, wherein the organic solvent used in the desulfonylation of step 5 is selected from: dimethylformamide, dimethylsulfoxide and N-methylpyrrolidinone.

36. The process as recited in Claim 35, wherein the organic solvent in step 6 is acetonitrile, tetrahydrofuran, or ether.

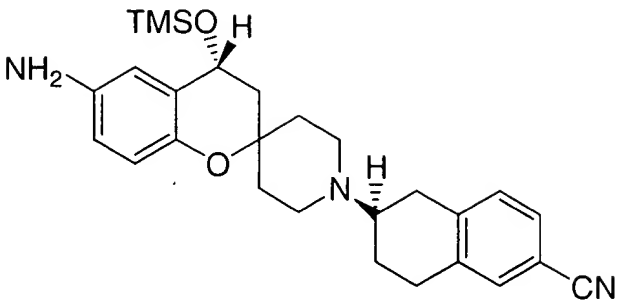
37. A process for the preparation of a radioligand compound of Formula I



I

comprising the steps of:

(a) reacting the amine



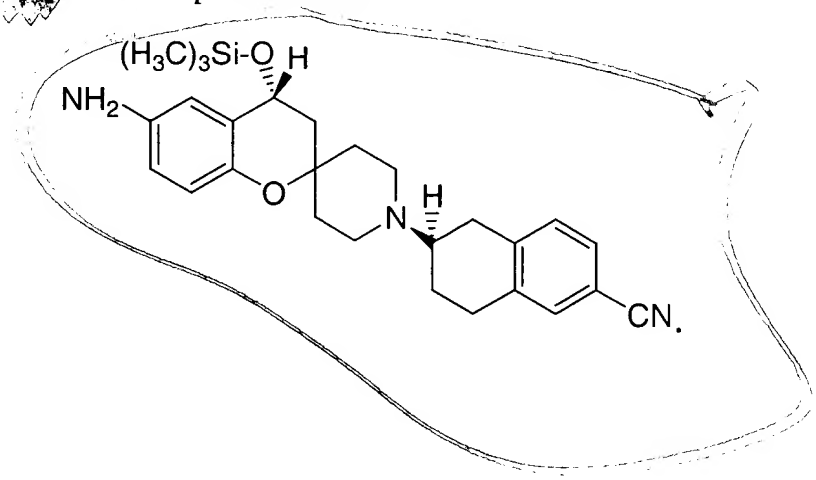
with [^{35}S]-methanesulfonyl chloride in the presence of an organic base to form the silyl-protected [^{35}S]-methanesulfonamide; and

(b) removing the silyl-protecting group of the silyl-protected [^{35}S]-methanesulfonamide with trifluoroacetic acid to give the radioligand compound of Formula I.

38. The process as recited in Claim 37, wherein the organic base is selected from triethylamine, trimethylamine, and diisopropylethylamine.

39. The process as recited in Claim 38, wherein the organic base is triethylamine.

40. A compound which is



Claim 1

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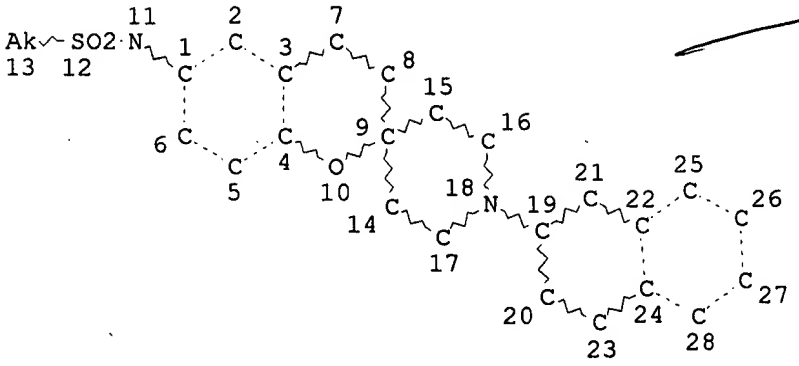

Parent structure
This application considered. 04/15/03 MEC

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NODE ATTRIBUTES:
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS  28

STEREO ATTRIBUTES: NONE
L3          156 SEA FILE=REGISTRY SSS FUL L1
L7              SCR 2039
L8            1 SEA FILE=REGISTRY SUB=L3 SSS FUL L7 AND L1
L10           1 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L8
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Screen for abnormal mass

← only one isotopically labelled structure found.

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L10  ANSWER 1 OF 1  HCAPLUS  COPYRIGHT 2003 ACS
ACCESSION NUMBER:         2002:71916  HCAPLUS
DOCUMENT NUMBER:          136:112612
TITLE:                    Radioligand and binding assay
INVENTOR(S):              Butcher, John W.; Claremon, David A.; Connolly, Thomas
                          M.; Dean, Dennis C.; Karczewski, Jerzy; Koblan,
                          Kenneth S.; Kostura, Matthew J.; Liverton, Nigel J.;
                          Melillo, David G.
PATENT ASSIGNEE(S):       Merck & Co., Inc., USA
SOURCE:                   PCT Int. Appl., 35 pp.
                          CODEN: PIXXD2
DOCUMENT TYPE:            Patent
LANGUAGE:                 English
FAMILY ACC. NUM. COUNT:   1
PATENT INFORMATION:

     PATENT NO.        KIND  DATE          APPLICATION NO.  DATE
     ---------------   ----  --------      ---------------  --------
     WO 2002005860      A1   20020124      WO 2001-US21731  20010710
         W:  AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN,
             CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,
             GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS,
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LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

US 2002034730 A1 20020321 US 2001-904045 20010712
PRIORITY APPLN. INFO.: US 2000-218397P P 20000714

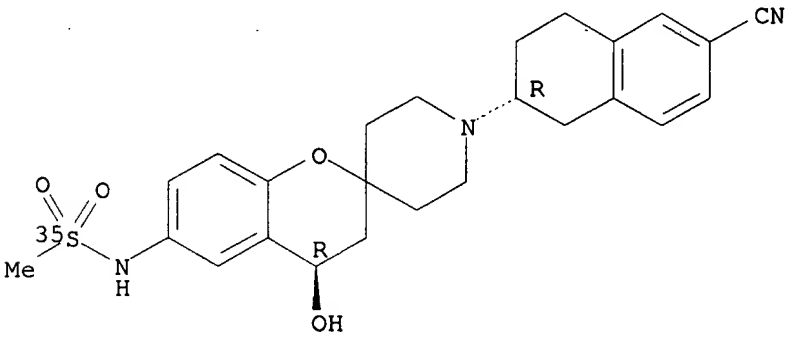
AB The present invention is directed to the radioligand compd., [35S]-radiolabeled (+)-N-[1 -(6-cyano-1,2,3,4-tetrahydro-2(R)-naphthalenyl)-3,4-dihydro-4(R)-hydroxyspiro[2H- -benzopyran-2,4 -piperidin]-6-yl]methanesulfonamide, its prepn., its use in characterizing an ion channel as an IKr channel, and its potential use in screening for Class III antiarrhythmic activity.

IT **390388-50-8P**
RL: BSU (Biological study, unclassified); BUU (Biological use, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of 35S-labeled IKr channel ligand as potential screening agent for antiarrhythmics)

RN 390388-50-8 HCAPLUS

CN Methanesulfonamide-35S, N-[(4R)-1'-[(2R)-6-cyano-1,2,3,4-tetrahydro-2-naphthalenyl]-3,4-dihydro-4-hydroxyspiro[2H-1-benzopyran-2,4'-piperidin]-6-yl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

2. Voltage is adjusted to 30% above threshold and resting tension is adjusted for maximum developed tension, and the tissue is allowed 5 min. reequilibration time.

3. Effective refractory period is measured at 1 Hz. Changes in resting tension and developed force are noted.

4. After equilibration, ERP's and developed force are measured at 30 minutes following the addition of increasing cumulative concentrations for test agent to the organ bath. Four to five concentrations of test agents were used to generate a concentration-response curve.

5. Four tissues per compound are tested.

Results

Employing the above protocol, it has been found that the effective concentration of most of the compounds of this invention required to increase the refractory period by an increment of 25% above base-line is less than or equal to 10 micromolar, i.e. $EC_{25} \leqq 10$ μM, whereas sotalol in the same protocol has an EC_{25} ~20 micromolar.

EXAMPLE 569

Preparation of intravenous solutions

A solution containing 0.5 mg of active ingredient per ml of injectable solution is prepared in the following manner.

A mixture of 0.5 mg of active ingredient is dissolved in 1 ml of acetate buffer. The pH is adjusted using hydrochloric acid or aqueous sodium hydroxide to about pH 5.5.

If it is desired that the intravenous solution be used for multi-dose purposes, 1.0 mg of methyl-p-hydroxy benzoate (methyl paraben) and 0.10 mg of n-propyl-p-hydroxy benzoate (propyl paraben) are mixed with the other solids before adding water to dissolve the solids. The solution is prepared and stored in such a manner that it is suitably protected from the deleterious effects of the atmosphere. One method by which this can be accomplished is by preparation and storage of the solution in an atmosphere of nitrogen. The resulting solution is sterilized by autoclaving, injectable solutions comprising 0.001, 0.01, and 0.1 mg, respectively, of active ingredient per ml of solution are similarly prepared substituting the indicated amount for the above-illustrated 10 mg quantity. Bulk injectable solutions of convenient volume for subsequent delivery in unit dosage form are readily prepared following the above procedure.

EXAMPLE 570

Tablet Preparation

Tablets containing 1.0, 2.0, 25.0, 26.0, 50.0 and 100.0 mg, respectively, of active ingredient are prepared as illustrated below.

TABLE FOR DOSES CONTAINING FROM 1–25 MG OF THE ACTIVE COMPOUND

	Amount - mg		
Active ingredient	1.0	2.0	25.0
Microcrystalline cellulose	49.25	48.75	37.25
Modified food corn starch	49.25	48.75	37.25
Magnesium stearate	0.50	0.50	0.50

TABLE FOR DOSES CONTAINING FROM 26–100 MG OF THE ACTIVE COMPOUND

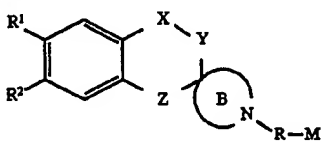
	Amount - mg		
Active ingredient	26.0	50.0	100.0
Microcrystalline cellulose	25.0	100.0	200.0
Modified food corn starch	2.21	4.25	8.5
Magnesium stearate	.39	0.75	1.5

All of the active compound, cellulose, and a portion of the corn starch are mixed and granulated to a 10% corn starch paste. The resulting granulation is sieved, dried and blended with the remainder of the corn starch and the magnesium stearate. The resulting granulation is then compressed into tablets containing 1.0 mg, 2.0 mg, 25.0 mg, 26.0 mg, 50.0 mg, and 100.0 mg of active ingredient per tablet.

While the foregoing specification teaches the principles of the present invention, with examples provided for the purpose of illustration, it will be understood that the practice of the invention encompasses all of the casual variations, adaptations, modifications, deletions, or additions of procedures and protocols described herein, as come within the scope of the following claims and its equivalents.

What is claimed is:

1. A compound of structural formula I:



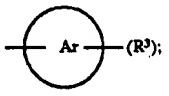
I

wherein:

X and Y are independently —O—, CHOH, —(CH_2)—;

Z is —O—;

M is



R is C_{1-6} alkyl;

R^1, R^2 and R^3 are independently H, —$NHSO_2(C_{1-6}$ alkyl), —CN;

B is a ring of 5 to 8 members; and

Ar is a single or fused ring carbocyclic or heterocyclic ring system containing up to 4 heteroatoms;

or a pharmaceutically acceptable salt thereof.

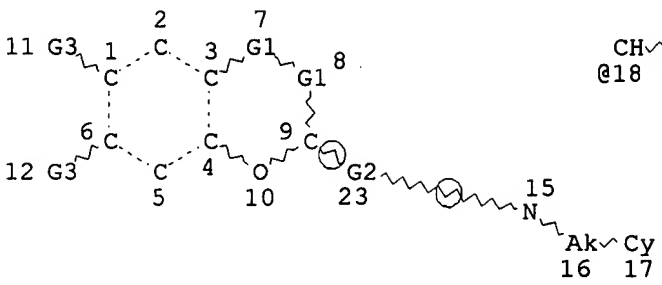
2. The compound of claim 1 which is N-{1'-(6-cyano-1,2,3,4-tetrahydro-2-napthalenyl)-3,4-dihydro-4-hydroxyspiro[2H-1-benzopyran-2,4'-piperidin-yl] methanesulfonamide.

3. A compound which is N-{1'-(6-cyano-1,2,3,4-tetrahydro-2-napthalenyl)-3,4-dihydo-4-hydroxyspiro[2H-1-benzopyran-2,4'-piperidinyl]methanesulfonamide, in the (R,R) form, the (R,S) form the (S,R) form, or the (S,S) form, or mixtures thereof, or a pharmaceutically acceptable salt thereof.

4. The compound of claim 3, which is in the (R,R) form.

5. A pharmaceutical composition comprising a pharmaceutical carrier, and dispersed therein, a therapeutically effective amount of a compound of claim 1.

=> d que
L16 STR



Considered 04/15/03 MJC

Claim
patno. 5,633,247

VAR G1=18/O/CH2
REP G2=(1-7) A
VAR G3=H/20/CN
NODE ATTRIBUTES:
CONNECT IS E4 RC AT 9
CONNECT IS E2 RC AT 16
CONNECT IS E1 RC AT 22
DEFAULT MLEVEL IS ATOM
GGCAT IS LOC AT 16
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 21

STEREO ATTRIBUTES: NONE
L17 4182474 SEA FILE=REGISTRY ABB=ON PLU=ON NR>3 AND NRS>1 AND N/ELS AND O/ELS
L23 38 SEA FILE=REGISTRY SUB=L17 SSS FUL L16
L27 43 SEA FILE=HCAPLUS ABB=ON PLU=ON "GENE, ANIMAL (L) ERG1"+OLD/CT

L28 1659832 SEA FILE=HCAPLUS ABB=ON PLU=ON L27 OR MEMBRANE OR ERG(3A)GENE ? OR (IKR OR I KR)(3A)CHANNEL? OR (293 OR CHO)(3A)CELL OR HEK OR RADIO? OR ISOTOP? OR LABEL?
L29 2 SEA FILE=HCAPLUS ABB=ON PLU=ON L23 AND L28

=> d l29 ibib abs hitstr hitind 1-2

L29 ANSWER 1 OF 2 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1994:524472 HCAPLUS
DOCUMENT NUMBER: 121:124472
TITLE: Determination of L-691,121, a new class III antiarrhythmic, and its principal metabolite in plasma by differential **radioimmunoassay**
AUTHOR(S): Greber, T. F.; Olah, T. V.; Gilbert, J. D.; Porras, A. G.; Hichens, M.
CORPORATE SOURCE: Merck Res. Lab., West Point, PA, 19486, USA
SOURCE: Journal of Pharmaceutical and Biomedical Analysis (1994), 12(4), 483-92
CODEN: JPBADA; ISSN: 0731-7085
DOCUMENT TYPE: Journal

LANGUAGE: English

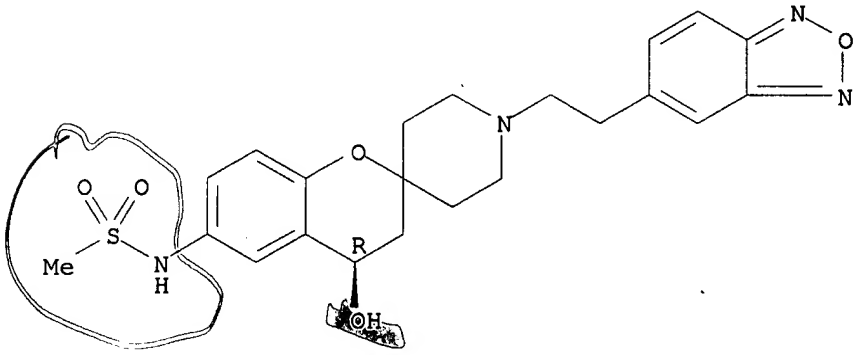
AB A sensitive and specific method based on RIA (RIA) has been developed for the anal. of L-691,121, a new antiarrhythmic agent, and its major metabolite, L-692,199, in plasma. Two RIAs using immunogens and **radioligands** prepd. from different derivs. of L-691,121 were used in conjunction to det. both parent compd. and metabolite concns. by solving simultaneous equations, since neither assay alone was adequately specific. Variable cross-reactivity factors were incorporated into the calcns. to correct for non-parallel drug and metabolite displacements curves. The direct assay using 30 .mu.L of plasma is sensitive to 0.1 ng mL-1 and has sufficient precision, accuracy and specificity for the anal. of clin. samples.

IT **149992-41-6**, L 692199
RL: ANT (Analyte); ANST (Analytical study)
(detn. of, in blood plasma by differential RIA)

RN 149992-41-6 HCAPLUS

CN Methanesulfonamide, N-[(4R)-1'-[2-(2,1,3-benzoxadiazol-5-yl)ethyl]-3,4-dihydro-4-hydroxyspiro[2H-1-benzopyran-2,4'-piperidin]-6-yl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



CC 1-1 (Pharmacology)

IT Immunoassay
(**radioimmunoassay**, L-691121 and metabolite L-692199 detn. by, in blood plasma)

IT 136075-60-0, L-691121 **149992-41-6**, L 692199
RL: ANT (Analyte); ANST (Analytical study)
(detn. of, in blood plasma by differential RIA)

L29 ANSWER 2 OF 2 HCAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 1993:551561 HCAPLUS

DOCUMENT NUMBER: 119:151561

TITLE: In vivo and in vitro metabolism studies on a class III antiarrhythmic agent

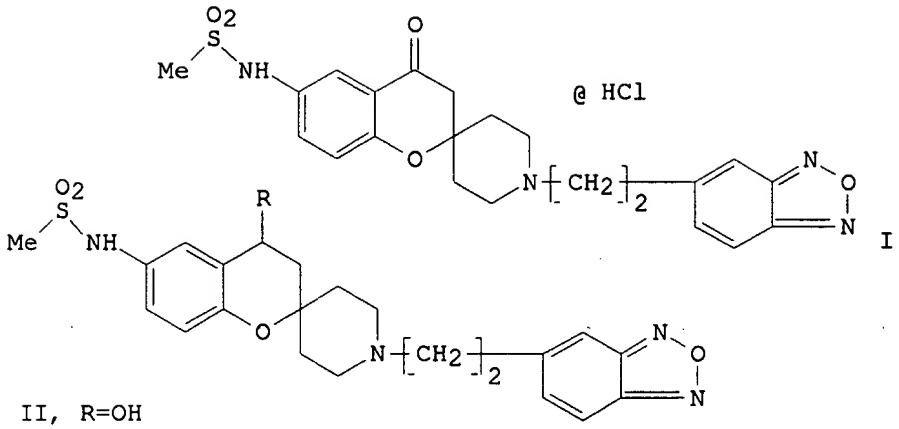
AUTHOR(S): Vickers, S.; Duncan, C. A.; Kari, P. H.; Homnick, C. F.; Elliott, J. M.; Pitzenberger, S. M.; Hichens, M.; Vyas, K. P.

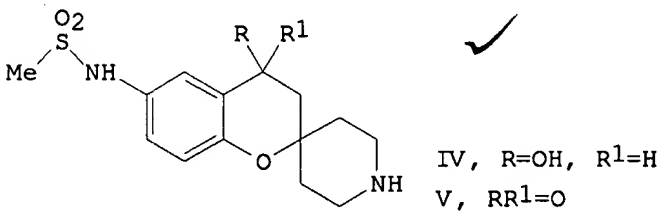
CORPORATE SOURCE: Dep. Drug Metab., Merck Res. Lab., West Point, PA, 19486, USA

SOURCE: Drug Metabolism and Disposition (1993), 21(3), 467-73
CODEN: DMDSAI; ISSN: 0090-9556

DOCUMENT TYPE: Journal

LANGUAGE: English
GI



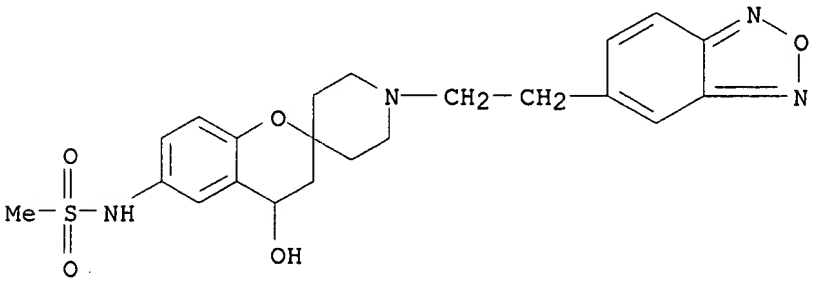


IV, R=OH, R1=H
V, RR1=O

AB The metab. of L-691,121 (I), a class III antiarrhythmic agent, was studied in vivo in rats and dogs and in vitro by using liver S9 or slices from these species and humans. After oral doses of [14C]I to rats (5 mg/kg) and dogs (1 mg/kg), urinary recoveries of **label** were, resp., 6% and 28%. Biliary excretion (0-24 h) accounted for 68% of a 5 mg/kg, po dose in rats and 19% of a 10 mg/kg dose, po in dogs. Metabolites were identified by application of FAB/MS, NMR, and diode-array UV spectroscopy. The major dog metabolites were the secondary alc. (II) produced by carbonyl redn. and its glucuronide conjugate (III). It was estd. that II and III represented 24 and 36%, resp., of the dog biliary **radioactivity**. After a 50 mg/kg dose of I, II represented .apprx.50% of the dog urinary **label**. A minor metabolite (IV) in dog urine was produced by redn. and loss of N-substitution. There were species differences in that, relative to dogs, II represented a much smaller fraction of the excreted dose in rats and there was no evidence for excretion of II in rats. N-Dealkylated I (V) was excreted, along with IV in rat bile. Dog liver slices and S9 fractions were most efficient (relative to human and rat liver tissues) at reducing I to II. Metabolic redn. of I to II was highly stereoselective and yielded the (-)-antipode as detd. by chiral chromatog.

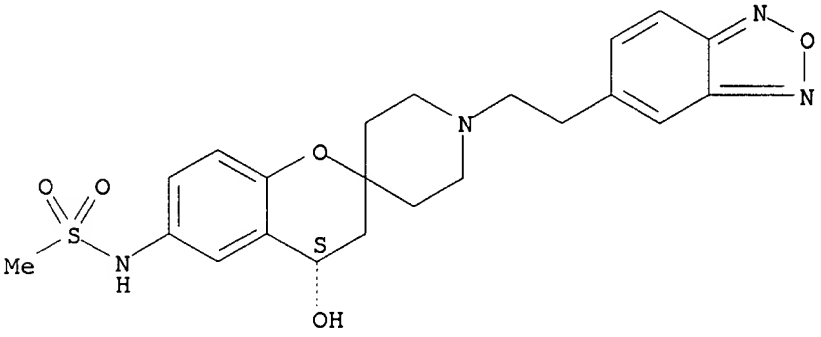
IT **136079-85-1 149969-96-0 149992-41-6**
RL: FORM (Formation, nonpreparative)
(formation of, as L691121 metabolite, in liver of humans and lab. animals, species differences in)

RN 136079-85-1 HCAPLUS
CN Methanesulfonamide, N-[1'-[2-(2,1,3-benzoxadiazol-5-yl)ethyl]-3,4-dihydro-4-hydroxyspiro[2H-1-benzopyran-2,4'-piperidin]-6-yl]- (9CI) (CA INDEX NAME)



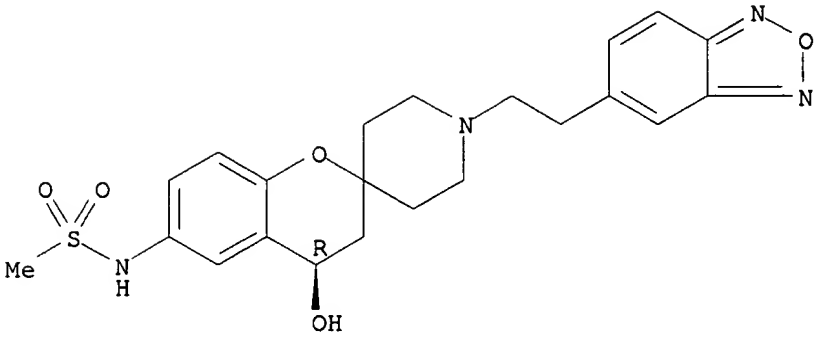
RN 149969-96-0 HCAPLUS
CN Methanesulfonamide, N-[1'-[2-(2,1,3-benzoxadiazol-5-yl)ethyl]-3,4-dihydro-4-hydroxyspiro[2H-1-benzopyran-2,4'-piperidin]-6-yl]-, (S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



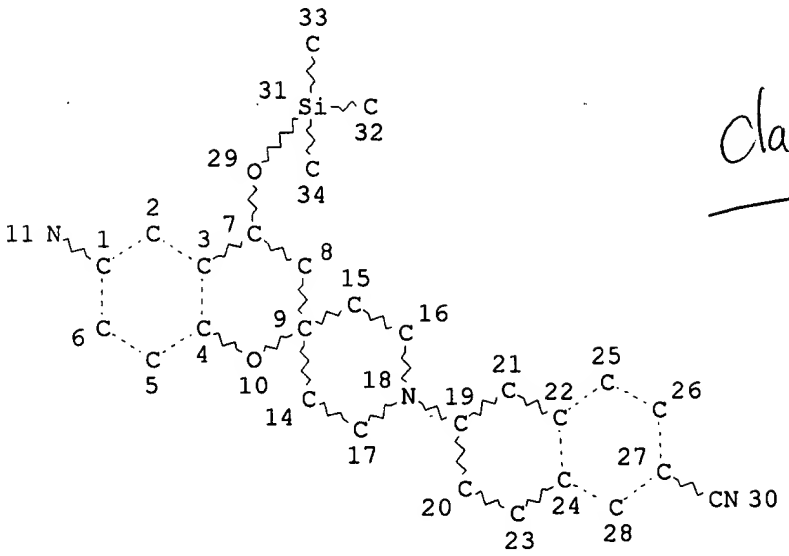
RN 149992-41-6 HCAPLUS
CN Methanesulfonamide, N-[(4R)-1'-[2-(2,1,3-benzoxadiazol-5-yl)ethyl]-3,4-dihydro-4-hydroxyspiro[2H-1-benzopyran-2,4'-piperidin]-6-yl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



CC 1-2 (Pharmacology)
IT **136079-85-1** 136081-93-1 149969-94-8 149969-95-9
149969-96-0 149992-41-6
RL: FORM (Formation, nonpreparative)
(formation of, as L691121 metabolite, in liver of humans and lab. animals, species differences in)

=> d que
L30 STR



Claim 40

considered
04/15/03
JC

NODE ATTRIBUTES:
CONNECT IS E1 RC AT 11
CONNECT IS E1 RC AT 32
CONNECT IS E1 RC AT 33
CONNECT IS E1 RC AT 34
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 32

STEREO ATTRIBUTES: NONE
L32 1 SEA FILE=REGISTRY SSS FUL L30
L33 1 SEA FILE=HCAPLUS ABB=ON PLU=ON L32

=> d ibib abs hitstr

L33 ANSWER 1 OF 1 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2002:71916 HCAPLUS
DOCUMENT NUMBER: 136:112612
TITLE: Radioligand and binding assay
INVENTOR(S): Butcher, John W.; Claremon, David A.; Connolly, Thomas M.; Dean, Dennis C.; Karczewski, Jerzy; Koblan, Kenneth S.; Kostura, Matthew J.; Liverton, Nigel J.; Melillo, David G.
PATENT ASSIGNEE(S): Merck & Co., Inc., USA
SOURCE: PCT Int. Appl., 35 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002005860	A1	20020124	WO 2001-US21731	20010710

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

US 2002034730	A1	20020321	US 2001-904045	20010712

PRIORITY APPLN. INFO.: US 2000-218397P P 20000714

this applic.

AB The present invention is directed to the radioligand compd., [35S]-radiolabeled (+)-N-[1 -(6-cyano-1,2,3,4-tetrahydro-2(R)-naphthalenyl)-3,4-dihydro-4(R)-hydroxyspiro[2H- -benzopyran-2,4 -piperidin]-6-yl]methanesulfonamide, its prepn., its use in characterizing an ion channel as an IKr channel, and its potential use in screening for Class III antiarrhythmic activity.

IT **390388-49-5P**

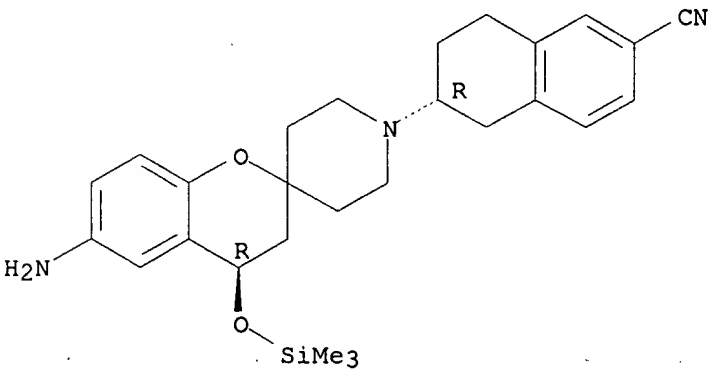
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(prepn. of 35S-labeled IKr channel ligand as potential screening agent for antiarrhythmics)

RN 390388-49-5 HCAPLUS

CN 2-Naphthalenecarbonitrile, 6-[(4R)-6-amino-3,4-dihydro-4-[(trimethylsilyl)oxy]spiro[2H-1-benzopyran-2,4'-piperidin]-1'-yl]-5,6,7,8-tetrahydro-, (6R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT